Conferences and Reviews

Antiplatelet Therapy—Part I

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We summarize current information about aspirin and other antiplatelet drugs in patients with cardiac and vascular disease. For each indication, we briefly summarize the rationale for the use of antiplatelet therapy and describe the findings of relevant clinical trials. We propose recommendations for the use of these agents in clinical practice. Part I covers the use of antiplatelet therapy for the primary and secondary prevention of myocardial infarction, coronary thrombolysis, unstable and chronic stable angina, and coronary artery–saphenous vein bypass grafts. In part II we review the use of antiplatelet agents in coronary angioplasty, atrial fibrillation, artificial cardiac valves, stroke, and peripheral vascular disease.

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The drugs used to inhibit platelet function are frequently prescribed in the United States today. The popularity of aspirin and other antiplatelet agents stems from a growing number of studies showing benefit in patients with atherosclerotic vascular disease and from the fact that the risks of therapy are considered by many to be low. Articles about antiplatelet therapy have been voluminous and often contradictory, making a careful and thoughtful assessment of the indications, risks, and benefits of antiplatelet therapy challenging at best for practicing physicians.

We concisely but critically review the indications and optimal use of antiplatelet therapy for patients with vascular and cardiac disease. When more information or discussion is required, readers are directed to several excellent reviews in which antiplatelet and other antithrombotic therapies are discussed in detail.[1-19]*

For each category of disease—for example, the secondary prevention of coronary heart disease—we discuss the rationale for the use of antiplatelet therapy, after which we briefly assess the major clinical trials that have strongly influenced recommendations for therapy. When appropriate, alternative forms of therapy, such as anticoagulants, are included. Finally, a set of recommendations has been formulated based on the information that is currently available.

While many of these recommendations may be almost universally accepted, others are controversial. In any event, each of the major trials is cited as well as analyses of these trials by others, allowing readers to probe more deeply into the subject with relative ease.

*See also "Use of Antiplatelet Agents in the Management of Thrombotic Disorders," by L. A. Harker, MD, on pages 426-427 of this issue.

Antiplatelet Agents

Aspirin

Aspirin's antithrombotic effects are thought to lie in its ability to inhibit platelet aggregation (but not platelet adhesion) by blocking the action of platelet cyclooxygenase and thereby reducing the cellular synthesis of thromboxane A_2.[20,21] Unfortunately, aspirin also inhibits endothelial cell prostaglandin synthesis and therefore reduces the release of prostacyclin. Because prostacyclin is thought to be a potent antiplatelet agent in vivo, this aspect of aspirin's action might lessen its therapeutic usefulness.

There seems to be little question that aspirin can be an effective antithrombotic agent.[22] Questions remain, however, as to the optimal dose, formulation, and schedule of administration for the prevention of thromboembolism in patients with vascular or cardiac disease. For example, clinical trials have been conducted using doses of aspirin ranging from 30 to more than 3,000 mg daily, all showing apparent benefit.

A surrogate marker for the possible efficacy of aspirin as an antithrombotic agent may be the relative inhibition of thromboxane compared with prostacyclin synthesis. At least on theoretic grounds, an optimal dose of aspirin would maximally inhibit platelet thromboxane synthesis but completely spare prostacyclin. Many studies have been done to examine this hypothesis. In general, it appears that lower doses of aspirin—60 to 325 mg a day—may be more effective than higher doses, less frequent administration (daily or every other day) may be better than several daily doses, and the use of very-low-dose sustained-release preparations may be the most effective.[23-27] Not all would concur with this interpretation of

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the data, however, particularly in the case of cerebrovascular disease in which a higher dose of aspirin might be superior to lower doses.[28] The incidence of bleeding complications may also be lower, but not absent, with smaller doses of aspirin.[29] In the final analysis, however, high-quality, randomized, controlled clinical trials will be necessary to determine the optimal regimens for aspirin therapy.

An interesting and possibly important facet of platelet function is that platelet reactivity may vary depending on the time of day. Platelet reactivity has been reported to be considerably increased in the early morning hours, although the mechanisms responsible for this finding are not known. This increase in activity has been associated with an increased risk of myocardial infarction and sudden cardiac death.[30] Ischemic stroke has also been reported to be more common in the morning.[31] Of interest, this increase in platelet reactivity may be suppressed by low doses of enteric-coated aspirin.[32]

Whether there is a sex difference in response to aspirin therapy remains unknown. Some studies have suggested that men have more platelet reactivity than women. It is not clear whether the doses of aspirin must be adjusted to accommodate these possible differences.[33,34]

As mentioned, a multitude of aspirin dosage schedules have been employed in the clinical trials published to date. It is reasonable to follow the dictates of the clinical trials in making recommendations for antiplatelet therapy, but in situations where optimal therapy is unclear, a general recommendation for aspirin therapy could include either 325 mg daily[35] or 325 mg every other day.[36]

Ticlopidine Hydrochloride

Ticlopidine is a thienopyridine derivative that has been shown to inhibit platelet aggregation, perhaps by blocking the exposure of glycoprotein IIb-IIIa fibrinogen binding sites on platelets.[37] Ticlopidine hydrochloride has been shown to be an effective antiplatelet agent in several clinical trials, but possible drawbacks of this therapy include a low incidence of neutropenia (<1% but usually reversible), an increase in serum cholesterol levels (about 10%), diarrhea (as many as 20% of patients), and a substantially greater cost than for aspirin.[37-40] Recently, a fatal syndrome resembling thrombotic thrombocytopenic purpura or hemolytic-uremic syndrome has been reported in four patients taking ticlopidine, with the symptoms occurring two to three weeks after starting therapy.[37,41] Ticlopidine has now been approved for use in patients with transient ischemic attacks who cannot tolerate aspirin. Additional clinical trials are warranted to compare ticlopidine use with that of aspirin to determine their relative efficacy and safety and to learn whether combining the two agents may be safe and provide increased therapeutic benefit.

Other Agents

Other antiplatelet agents that have been thoroughly studied include dipyridamole and sulfinpyrazone.[25,26] Most investigators have concluded that these agents are not as effective as aspirin, and their use has gradually diminished over the past decade.[42]

Primary Prevention of Myocardial Infarction

Rationale

Myocardial infarction commonly results from acute coronary artery occlusion by platelet thrombus at the site of a ruptured atherosclerotic plaque.[43] Unfortunately, many patients with acute coronary artery occlusion have no warning symptoms, which precludes early diagnosis and treatment. Antiplatelet therapy has been shown to be successful in reducing platelet-mediated thromboses in various experimental models.[44] Platelet inhibitory therapy, such as low-dose aspirin, is relatively safe and inexpensive.

Major Clinical Trials

The Physicians' Health Study was a placebo-controlled, blinded, randomized clinical trial involving 22,071 male physicians.[36] Participants received aspirin, 325 mg every other day, or a placebo tablet. Those physicians older than 50 years who were taking aspirin had a statistically significant 44% reduction in the first occurrence of fatal and nonfatal myocardial infarction, although overall death rate from cardiovascular causes was not changed (relative risk = 0.96). The relative risk of fatal and nonfatal myocardial infarction with low-dose aspirin therapy was 0.56 ($P << .01$). There was a small but not significant increase in the incidence of stroke, mainly because of the subgroup with hemorrhagic stroke (relative risk = 2.14, $P = .06$).

The British Doctors' Trial included 5,139 physicians whose ages ranged from 50 to 78 years.[45] This trial was randomized but was not placebo controlled and extended for six years. Treated subjects received 500 mg of aspirin a day, whereas the controls were asked to refrain from taking aspirin. A trend (nonsignificant) was found for a decrease in the myocardial infarction incidence. The statistical confidence intervals did not exclude a 25% reduction in the incidence of myocardial infarction by aspirin. Total mortality was 10% lower in the aspirin group, but this did not reach significance. The incidence of disabling strokes was slightly but significantly increased in the aspirin-treated patients ($P = .05$).

Considering both primary prevention trials together, there was a significant reduction in the incidence of nonfatal myocardial infarction of about a third ($P << .01$).[46] There was no significant difference in the number of cerebrovascular events, but a nonsignificant increase in the incidence of disabling stroke was found. Neither trial, nor the trials taken together, had the power to assess the effect of aspirin therapy on overall mortality.

The Nurses' Prospective Cohort Study was a nonrandomized trial of a group of 87,678 registered nurses ranging in age from 34 to 65 years and free of baseline disease for six years.[47] Women who reported taking one to six aspirin tablets per week (but not more) had a relative risk

of a first myocardial infarction that was 0.68 ($P < .01$) compared with women who did not take aspirin. When other risk factors for coronary artery disease were included in the analysis, the relative risk in the aspirin group was 0.75 ($P < .05$). The risk reduction for women 50 years of age or older was 0.61 ($P < .01$). There was no alteration in the risk of stroke.

Recommendations

- Men older than 50 years who have substantial coronary risk factors—such as a strong family history of coronary artery disease, hyperlipidemia, or diabetes mellitus—should take one 325-mg aspirin tablet every other day.
- Men older than 50 without risk factors should not take aspirin on a regular basis. Aspirin therapy, however, can be considered for men who are younger than 50 years who have strong coronary risk factors, although there is as yet no direct evidence from clinical trials of benefit from this therapy.
- Women older than 50 years who have coronary risk factors may benefit from taking one tablet daily or one every other day—although benefit has not yet been shown in a prospective, randomized clinical trial.
- Aspirin therapy should not substitute for the aggressive management of other coronary risk factors such as smoking, hyperlipidemia, lack of exercise, diabetes mellitus, or systemic hypertension.

Secondary Prevention of Myocardial Infarction

Rationale

As mentioned in the previous section, platelet-mediated thrombosis is often responsible for acute coronary artery occlusion, and this process may respond to antiplatelet therapy. Moreover, several recent studies have suggested that platelet reactivity and mean platelet volume may be increased in some patients following myocardial infarction and that these findings may predict future coronary artery occlusion.[48-51]

Major Clinical Trials

The Antiplatelet Trialists Collaboration did a meta-analysis of 25 trials of prolonged antiplatelet treatment of patients with a history of coronary artery disease, transient ischemic attacks, or stroke.[35] Data from a total of 29,000 patients were included in the study, of whom 3,000 died. The analysis showed that various regimens of antiplatelet therapy significantly reduced mortality from vascular causes by 15%, the incidence of stroke or myocardial infarction by 30%, and that of overall vascular events by 25%. There was no apparent effect on mortality due to nonvascular causes. The reductions in three separate end points—nonfatal myocardial infarction, nonfatal stroke, and the total number of deaths due to cardiovascular disease—were significant in the antiplatelet treatment groups ($P << .01$). All-cause mortality was also reduced ($P << .01$). The authors concluded that higher doses of aspirin conferred no more benefit than 325 mg daily.

The Second International Study of Infarct Survival (ISIS-2 trial) enrolled 17,187 patients in a multicenter study of patients presenting with clinically suspected myocardial infarction who were treated with 1.5 million units of intravenous streptokinase, aspirin (160 mg daily), both, or neither therapies.[52] After five weeks, mortality in the groups receiving aspirin was decreased by 23% compared with placebo ($P << .01$) and the reinfarction rate was decreased by 50%. The benefit of aspirin therapy was still apparent 15 months later ($P < .01$). No increase in the incidence of cerebral hemorrhage was found in the aspirin-treated patients.

Alternative Treatment

Two clinical trials of high-intensity (international normalized ratio* of 3 to 5) oral anticoagulants, the 60-Plus Reinfarction Study of 1980 and the Norwegian Anticoagulant Study of 1990, showed significant reductions in the incidence of myocardial infarction, stroke, and death in the patients receiving anticoagulants after two to three years of treatment.[54,55]

Recommendations

- Patients presenting with acute myocardial infarction should receive 160 mg of aspirin immediately and daily thereafter while in the hospital. Aspirin should be given whether or not the patient is a candidate for treatment with thrombolytic agents.
- All patients with acute myocardial infarction should receive long-term therapy with 325 mg of aspirin daily, unless there is a contraindication to its use. Aspirin therapy should be continued for at least two years and probably indefinitely.
- Alternatively, patients could be treated with high-intensity warfarin sodium anticoagulation—international normalized ratios of 3 to 4.5—although the increased risk of bleeding may offset some of the benefits of this form of therapy. If there are other indications for anticoagulants (such as dilated cardiomyopathy), then warfarin should probably take precedence over aspirin therapy.

Antiplatelet Therapy After Coronary Artery Thrombolysis

Rationale

A recurrence of thrombosis is a major problem after successful coronary artery thrombolysis and has been found to occur in 5% to 20% of patients.[56] Potent thrombogenic stimuli include residual unlysed thrombus and the surface of the ruptured coronary artery plaque. In addition, a major product of activated platelets, thromboxane A_2, is markedly increased in amount during and after coronary thrombolysis using streptokinase or tissue plasminogen activator.[57,58] An increased concentration of thromboxane metabolites is present in the urine during the procedure and for as long as 48 hours afterwards. The site of platelet activation is unknown but may be the

*The international normalized ratio is a standardized method of reporting prothrombin times to ensure that a uniform intensity of oral anticoagulant therapy is used worldwide.[53]

reperfused coronary artery bed. Antiplatelet therapy might inhibit platelet reactivity and thereby reduce the rate of rethrombosis in the days or weeks following thrombolysis.

Major Clinical Trials

The large multicenter ISIS-2 study involving more than 17,000 patients showed that thrombolytic therapy with streptokinase, when given with aspirin—160 mg daily for a month—resulted in a 42% decline in the number of vascular deaths five weeks later compared with the administration of streptokinase alone ($P << .01$).[52] Aspirin therapy also decreased the rate of nonfatal reinfarction. No increased incidence of bleeding was seen with the combination therapy. The principal findings of the study were unchanged at 15 months.

In the Heparin–Aspirin Reperfusion Trial Study, heparin (a 5,000-unit bolus followed by a continuous infusion) appeared to be a more effective antithrombotic agent than low doses (80 mg) of aspirin when given in conjunction with recombinant tissue plasminogen activator for thrombolysis.[59] Angiograms obtained 7 to 24 hours after thrombolysis showed an 82% patency rate in the patients assigned to receive heparin, compared with 52% in the aspirin group ($P < .01$). In contrast, aspirin therapy was at least as effective as the use of heparin in preventing reocclusion between days 1 and 7 after thrombolysis. A question might be raised, however, as to whether an adequate dose of aspirin was used at the start of the fibrinolytic therapy.

The European Cooperative Study Group examined the effects on infarct size and left ventricular function of the administration of tissue plasminogen activator, aspirin, or heparin.[60] When all three drugs were used, there was a statistically significant 20% reduction in the size of the infarct as reflected in serum enzymes. In addition, the ejection fraction was 2.2% higher in this group ($P < .01$). Only 18 of 47 deaths occurred in patients receiving the three drugs, whereas 29 deaths occurred in the group of patients receiving only aspirin or heparin. The 51% reduction in mortality failed to reach statistical significance, however, because of the small number of patients enrolled in the study.

Recommendations

- Aspirin, 160 to 325 mg, should be given as soon as possible when a diagnosis of acute myocardial infarction is made and thrombolytic therapy is being considered.
- Intravenous heparin, given first as a bolus and then followed by a continuous infusion, should be administered along with thrombolytic therapy.
- If surgical revascularization is not required, then the use of aspirin, 325 mg daily, is recommended indefinitely for the secondary prevention of myocardial infarction. There are no data available as yet to suggest that aspirin therapy reduces the incidence of late coronary artery reocclusion following thrombolysis.

Unstable Angina

Rationale

As shown by coronary angioscopy, the pathogenesis of unstable angina is thought to involve the formation of platelet thrombi on the surface of disrupted atherosclerotic plaques, which intermittently produces vascular occlusion.[61] The activation of platelets may also reduce blood flow by the release of vasoconstrictors such as thromboxane A_2, whose effects may be augmented by a loss of vasodilators such as prostacyclin or endothelium-derived relaxing factor from the damaged vascular surface.[62] Because platelets appear to play an important role in the pathogenesis of unstable angina, therapy to inhibit platelet aggregation seems appropriate and rational.

Major Clinical Trials

The Veterans Administration Cooperative Study was a multicenter, double-blind, randomized, placebo-controlled trial that evaluated 1,266 men with unstable angina.[63] Patients were given buffered aspirin, 325 mg daily, or placebo for 12 weeks. The incidence of nonfatal myocardial infarction or death was 51% lower in the aspirin-treated group ($P < .01$), and total mortality was also decreased by 51% ($P = .05$). The benefits of aspirin therapy persisted for the ensuing year.

The Canadian Multicenter Trial examined 555 (74% male) patients with unstable angina who received 325 mg of aspirin four times a day, sulfinpyrazone, 200 mg four times a day, both drugs, or placebo for 18 months.[64] The relative risk of death due to cardiac disease and of nonfatal myocardial infarction in the patients receiving aspirin was reduced by 51% ($P < .01$). A risk reduction of 71% was found when death from cardiac disease alone or from any cause was considered ($P < .01$).

The Montreal Heart Institute Trial compared the administration of aspirin, 325 mg twice a day, heparin, 1,000 units per hour, aspirin plus heparin, or placebo in 479 patients with unstable angina.[65] Patients were entered into the study eight hours after their last episode of pain and were treated for six days. Aspirin use decreased the rate of myocardial infarction by 72% ($P < .05$) compared with 89% for heparin ($P < .01$). The combination of heparin plus aspirin was no better than either alone, but resulted in an increased incidence of bleeding.

The Ticlopidine Trial was an open, non-placebo-controlled trial that studied 652 patients who were given either conventional therapy (without aspirin) or conventional therapy plus ticlopidine in a dose of 250 mg twice a day.[66] Treatment was begun within 40 hours, and patients were observed for six months. The incidences of death due to cardiovascular events and nonfatal myocardial infarction combined were reduced from 13.6% to 7.35% in these patients, a risk reduction of 46.3% ($P < .01$). The relative risk of dying of cardiovascular disease alone was 0.47, which did not reach significance ($P = .14$).

The RISC Group [Research on Instability in Coronary Artery Disease] studied 796 men with unstable angina or non–Q-wave myocardial infarction in a double-

blind, placebo-controlled trial for a year.[67] Treatment consisted of 75 mg of aspirin taken orally with or without five days of intermittent intravenous heparin therapy. In this study, the use of aspirin reduced the risk of myocardial infarction and death. After five days, the risk ratio was 0.43 ($P < .05$); by one month it was 0.31 ($P << .01$), and after three months it was 0.36 ($P < .01$). This trial was unique in that moderately low doses of aspirin (75 mg) were used.

Finally, aspirin in a dose of 75 mg daily or placebo was given in a double-blind randomized trial to 796 men with unstable angina or non–Q-wave myocardial infarction in Sweden.[68] The risk ratio of myocardial infarction or death was significantly reduced after one year of therapy to 0.52 ($P << .01$), as was the rate of severe angina necessitating coronary angioplasty (risk ratio at 1 year = 0.71). There was no increased rate of bleeding. A subgroup analysis was done of patients who continued to have evidence of ST-segment depression but who did not have angina (silent ischemia) following an episode of unstable angina.[69] The aspirin treatment substantially reduced the risk of subsequent myocardial infarction or death over the ensuing year in the group with silent ischemia (4% versus 21%, $P < .01$ at 3 months; 9% versus 28%, $P < .01$ at 12 months).

Alternative Therapies

The Montreal Heart Institute trial of unstable angina (discussed earlier) examined the effect of heparin given at a rate of 1,000 units per hour following a bolus infusion of 5,000 units for six days after hospital admission.[65] Heparin use was highly effective in preventing refractory angina ($P < .01$) as well as myocardial infarction ($P < .01$). When heparin therapy was combined with the use of aspirin, the rate of serious bleeding was slightly increased (3.3% versus 1.7% with heparin alone).

A recent study by Neri Serneri and co-workers examined the effect of treatment with heparin compared with aspirin or recombinant human tissue plasminogen activator in 399 patients with refractory unstable angina.[70] After a bolus of 5,000 units, heparin was infused at a rate of 1,000 units per hour, with the dose adjusted to maintain the partial thromboplastin time 1.5 to 2.0 times baseline. Over the first three days of therapy, the heparin infusion significantly ($P < .01$) decreased the frequency of angina by 84% to 94%, silent ischemia by 71% to 77%, and the overall duration of ischemia by 81% to 86%. The use of bolus heparin alone, aspirin, or recombinant tissue plasminogen activator was not effective. Only minor bleeding occurred.

Recommendations

Patients presenting with acute chest pain may pose a problem in management because the ultimate diagnosis, such as unstable angina or myocardial infarction, may not be immediately clear. As a consequence, recommendations for optimal antithrombotic treatment may be difficult. Some guidelines are suggested, however, based on published clinical trials and current clinical practice:

- In patients with a clear history of unstable angina, immediate therapy with heparin—a 5,000-unit bolus, followed by an infusion of 1,000 units per hour—should be considered. If myocardial infarction does not occur and invasive procedures are not warranted, then aspirin therapy, 325 mg daily, may be started when the use of heparin is discontinued. If refractory unstable angina develops, then heparin therapy can be continued, with laboratory monitoring to maintain the partial thromboplastin time at 1.5 to 2.0 times control.
- If acute myocardial infarction is found, aspirin therapy, 160 mg, can be started along with a consideration of thrombolytic therapy (see earlier discussion). If thrombolytic agents are not used, aspirin therapy may be continued.
- If urgent percutaneous transluminal coronary angioplasty is elected, a regimen of aspirin, 160 to 325 mg daily, can be started before the procedure and continued thereafter (discussed later).
- If urgent coronary artery bypass grafting is indicated, the administration of aspirin should be withheld until the immediate postoperative period (discussed later). If aspirin has been given, however, increased operative bleeding should be anticipated.[71,72]
- In all patients, long-term therapy with aspirin, 325 mg a day, should be considered for secondary prophylaxis of cardiovascular disease.

Chronic Stable Angina

Rationale

In contrast to its role in unstable angina, there is no convincing evidence that platelet-mediated coronary artery thrombosis is responsible for recurrent chest pain in patients with chronic stable angina. Angioscopy has not shown platelet thrombi in these patients.[61] Some studies, however, have suggested that platelets may be activated during or shortly after episodes of angina.[12] Increased urinary excretion of thromboxane metabolites has recently been found in patients with stable angina.[73] The annual mortality for stable exertional angina is approximately 4%, and myocardial infarctions develop in patients with stable exertional angina at a rate of 5% per year.[74]

Major Clinical Trials

Investigators from the Physicians' Health Study analyzed the efficacy of low-dose aspirin therapy in a subgroup of physicians who were previously known to have baseline chronic stable angina but no history of myocardial infarction or transient ischemic attacks.[75] The subjects received 325 mg of aspirin or placebo every other day and were observed for 60 months. The relative risk of myocardial infarction in the aspirin-treated group was significantly reduced to 0.3 ($P < .01$). Their overall cardiovascular risk was reduced by 87% ($P < .01$). There was an increase in the relative risk of stroke of 5.4 ($P < .05$), although none of the strokes were fatal.

In the Swedish Angina Pectoris Aspirin Trial, 2,035 patients (52% male) with chronic stable angina were ran-

domly allocated to taking aspirin, 75 mg daily, or placebo, and outcome events for the ensuing 50 months were then assessed.[76] All patients were given sotalol hydrochloride to control symptoms. The incidence of primary events of subsequent myocardial infarction and sudden death was reduced by 34% in the aspirin group ($P < .01$). The incidence of major hemorrhage was similar in the two groups—aspirin group, 20 patients; placebo group, 13 patients.

Another subgroup analysis of the Physicians' Health Study sought to determine whether administering low-dose aspirin on alternate days could prevent the occurrence of angina pectoris.[77] The relative risk of confirmed new-onset angina in the aspirin group was found to be 1.1. Therefore, this trial found that low-dose aspirin therapy did not reduce the incidence of angina pectoris in previously asymptomatic men.

Recommendations

- Therapy with low doses (325 mg) of aspirin is recommended for men with chronic stable angina for the prevention of myocardial infarction and to reduce the overall cardiovascular risk. A substantially reduced incidence of myocardial infarction, however, must be balanced with a slightly increased risk of nonfatal stroke that was reported in one study.[75]

Coronary Artery-Saphenous Vein Bypass Grafts

Rationale

The postsurgical occlusion of coronary artery-saphenous vein bypass grafts is rather common. During the first month after the operation, approximately 12% of grafts and distal anastomoses will occlude. This complication increases to about 20% at six months. By one year, 41% to 47% of patients will have one or more failed grafts.[12]

During the first month after the operation, vein graft occlusion is most often the result of thrombosis, which is likely to be platelet mediated. In contrast, late occlusion results from intimal proliferation, which may also involve platelets.[78] Studies have suggested that radiolabeled platelet survival was normal in patients whose grafts remained open, whereas platelet survival was shortened in patients whose grafts occluded.[79] Because both early and late occlusion appear platelet mediated, antiplatelet therapy might be effective in maintaining graft patency.

Major Clinical Trials

In 1982 a prospective, randomized, double-blind trial was reported from the Mayo Clinic (Rochester, Minnesota) in which patients undergoing a saphenous vein bypass graft procedure were given dipyridamole, 400 mg a day for two days preoperatively, followed by aspirin, 325 mg daily, beginning seven hours postoperatively by nasogastric tube.[80] Thereafter, patients received 325 mg of aspirin and 75 mg of dipyridamole three times a day. Within a month of the operation, 8% of the patients given the antiplatelet therapy had at least one distal vein graft occluded, whereas grafts were occluded in 20% of patients receiving placebo ($P < .01$). By one year, the incidence of late graft occlusions was significantly reduced from 14% to 9% by the antiplatelet therapy.[81]

The first Veterans Administration Cooperative Study was a prospective, randomized, double-blind study of 772 patients that showed that aspirin given once a day was as effective as aspirin given three times a day in preventing graft occlusion.[82] Neither dipyridamole nor sulfinpyrazone therapy was found to be effective, however. When aspirin therapy was begun 12 hours before the operation, perioperative bleeding was observed, with increased rates of reoperation.[71,72] In this study, the aspirin-treated patients had early graft patency of 94% versus 85% in the placebo group ($P < .05$). After one year, aspirin therapy remained effective, with 23% of grafts occluded in the placebo group compared with 16% in the treated groups ($P < .01$).[83] There was no difference in occlusion rate in vessels greater than 2 mm in diameter. A more recent study from the same group documented that an aspirin regimen started six hours after the operation was equally protective for early graft patency—7 to 10 days—as aspirin administered the night before the operation.[84]

A meta-analysis was done using data from several studies of antiplatelet therapy for coronary artery-saphenous vein graft occlusion performed from 1966 to 1988.[85] It should be noted that all of the studies showed a beneficial effect of antiplatelet therapy, although not all reached statistical significance. The meta-analysis clearly showed that active treatment with antiplatelet therapy was beneficial (overall effect size was 0.3, a significant effect) and that efficacy improved with the early initiation of treatment.

In another Veterans Administration Cooperative Trial, internal mammary artery or saphenous vein grafts to the left anterior descending coronary artery were studied.[86] Patients received either 325 mg of aspirin a day, aspirin three times a day, aspirin plus dipyridamole, 75 mg three times a day, or placebo. The aspirin therapy was started either 6 or 12 hours before the operation. There were no differences in patency rates of either internal mammary artery or saphenous vein grafts with aspirin treatment at one year in these higher flow vessels.

A multicenter, randomized, double-blind, placebo-controlled trial compared a regimen of 50 mg of aspirin given three times a day, 50 mg of aspirin plus 75 mg of dipyridamole three times a day, or placebo in 1,112 patients undergoing a coronary artery-vein graft operation.[87] All patients received 100 mg of dipyridamole four times a day for 48 hours before the operation, with the assigned treatment regimen begun seven hours after the operation. Vein graft angiography was carried out at ten days. The early occlusion rate for distal anastomoses was reduced from 18% in the placebo group to 12.9% in the aspirin-plus-dipyridamole group ($P < .05$).

Recommendations

- Aspirin should be given in a dose of 325 mg a day by nasogastric tube beginning immediately after the operation (within 6 hours). The preoperative administration of aspirin has been associated with excessive bleeding. Although it is not clear that it is beneficial, dipyridamole at a dose of 400 mg per day can be given two days before the procedure but should be discontinued afterwards.
- Aspirin should continue to be administered at that dose for at least three months and probably indefinitely.
- Internal mammary artery or saphenous vein grafts to the left anterior descending artery alone probably do not require antithrombotic therapy. The administration of aspirin may, however, be indicated for underlying coronary artery disease (see recommendations for secondary prevention).

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